## REMARKS

Claims 1 to 29 were previously cancelled. Claims 30 to 35 are currently pending and under examination. Claims 30 and 31 are amended. No new matter is presented by virtue of the within amendments; support therefor can be found throughout the specification and original claims of the application. For instance, on page 15 of the specification.

Turning to the Office Action, claims 30-35 stand rejected under 35 USC §103(a) over Kawada (1998) and Aoki et al. (1998).

The rejection is traversed. The cited documents, even in combination, fail to teach or suggest the features of the present invention and cannot therefore sustain the rejection.

The Examiner asserts at page 2 of the Office Action that Kawada teaches a bioreactor. On page 3, the Examiner notes that in the bioreactor of Kawada, "The ***continuous flow*** through the matrix [to which the cells are attached] generates a beneficial concentration gradient of oxygen and nutrients while preventing excessive shear stresses or build up of waste products (see Introduction)." [emphasis added] Applicant has amended the claim 30 as set forth above to recite that circulation of the culture media is stopped for an extended period of time, 2 to 10 hours, and that the addition of fresh culture media be limited during specific phases of hepatitis C infection of the cells. Applicant has amended claim 31 to recite that the supply rate of oxygen be increased to the cells 1.5- to 2.5-fold for 30 minutes to 2 hours immediately prior to the addition of the virus to the cells. This step is neither taught nor suggested by either of the references, even in combination.

As noted by the Examiner, Kawada focuses on the essential aspect of providing ***continuous flow*** of media in the bioreactor for conditions of optimal cell growth the growth of hepatic cells. Kawada notes the shortcomings of the prior bioreactors on page 109. Specifically, Kawada states:

> Conventional hollow fiber or spheroid culture systems suffered from stacking cells upon each other, causing cell death within the colony mass,

> and ***preventing the free flow of liquid media through the matrix***. [emphasis added]

This point is further emphasized by Kawada on the second column on page 110 which states:

> In conventional hollow fiber or bead (not pourous) culture systems, cells affix to the surface of the fibers or beads and proceed to become flattened and stacked, ***making it difficult for each cell to obtain its required quantities of oxygen and nutrients***. [emphasis added]

Kawada repeatedly states the advantage of the system taught in therein. For example, on page 11, column 2, Kawada states:

> This ***continuous flow*** through the matrix [in the radial flow bioreactor] generates a ***beneficial concentration gradient of oxygen and nutrients*** while ***preventing*** excessive shear stress or ***buildup of waste products***. [emphasis added]

The point is further emphasized on page 112, column 2, which states:

> Clear intracellular spaces can be confirmed, ***enabling free flow of the liquid medium*** throughout the matrix, thereby providing an ***even distribution of oxygen and nutrients***, as well as ***preventing buildup of waste products***. [emphasis added]

The methods of use of the bioreactor of Kawada neither teach or suggest the instantly claimed methods in which the ***flow of media is not continuous***. The amendment of claim 30 to recite that the circulation of the culture media is stopped for 2 to 10 hours, clearly longer than would be required to obtain a sample of media or than would ever be desired by Kawada. A pause in circulation for such and extended period of time would result in an uneven distribution of oxygen and nutrients and result in a buildup of waste products. This goes directly against the teachings of Kawada.

Claim 31 recites a specific increase in the supply rate of fresh media and oxygen to the cells immediately prior to infection. The methods of Kawada do not teach infection, and could not provide a teaching or suggestion of modulating the supply rate of fresh media and oxygen in relation timing of infection.

The Examiner asserts that "Aoki et al teach and in vitro system that successfully supports the efficient growth of HCV via the FLC4 cell line." Further, the Examiner asserts that "it would have been obvious to the ordinary artisan to combine the two teachings above in order to perform a method of proliferating HCV using FLC4 cell line and the disclosed bioreactor. " (page 4) Applicant respectfully disagrees.

As noted above, Kawada teaches that cells must be grown with a ***continuous flow*** of media. Kawada does not teach any methods of infection. Aoki teaches infection of cells grown in 12-well plates. ***Media can not be circulated in a 12-well plate***. Further, the "rate" of supplying fresh media or oxygen cannot be changed in a 12-well plate. Aoki teaches that after addition of the virus, the inocula should be removed after 60 minutes and replaced with fresh media. This is clearly distinct from the instantly claimed methods.

Applicant submits that the cited references, even in combination, fail to teach or suggest the instantly claimed methods in which circulation of media is stopped after infection, or in which the rate of delivery of media and oxygen is increased at specific times relative to the infection of the cells.

To properly determine a *prima facie* case of obviousness, the Examiner "must step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made." M.P.E.P § 2142. This is important as "impermissible hindsight must be avoided and the legal conclusion must be gleaned from the prior art." Id. Four factual inquiries must be made: first, a determination of the scope and contents of the prior art; second, a determination of the differences between the prior art and the claims in issue; third, a determination of level of ordinary skill in the pertinent art; and fourth, an evaluation of evidence of secondary consideration. *Graham v. John Deere*, 383 U.S. 1, 17-18, 148 USPQ 459, 467 (1966). Three criteria may be helpful in determining whether claimed subject mater is obvious under 103(a): first, if there is some suggestion or motivation to modify or combine the cited references; second, if there is a reasonable expectation of success; and third, if the prior art references teach or suggest all the claim limitations. *KSR Int'l Co. v. Teleflex, Inc.* No 04-1350 (U.S. Apr. 30, 2007). With regard to the first criterion,

the mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.3d 690 (Fed. Cir. 1990). "Knowledge in the prior art of every element of a patent claim ... is not of itself sufficient to render claim obvious." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1333-34 (Fed. Cir. 2002)]. The issue is whether there is an apparent reason to combine the known elements in the fashion claimed by the patent at issue. *KSR Int'l Co. v. Teleflex, Inc.*

For at least the reasons set forth herein, Applicant respectfully submits that a *prima facie* case of obviousness has not been established under the requirements of 35 U.S.C. §103(a). Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

## CONCLUSION

In view of the above amendments and remarks, Applicant believes the pending application is in condition for allowance.

## FEE AUTHORIZATION

While no fees are believed to be due, the Commissioner is authorized to charge any fees associated with this submission to our Deposit Account, No. 04-1105, Reference 56972(303842). Any overpayment should be credited to said Account.

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Respectfully submitted,

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